Exhibit 1

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875** **Honorable Renée Marie Bumb, Chief Judge**
This Document Relates to Gaston J. Roberts, Jr., and wife Jan Roberts | Case No. 1:20-cv-00946-RBK-JS	**EXPERT REPORT OF ANDREW THOMPSON, PH.D.**

I have been asked to review and respond to certain statements made in expert reports submitted by Drs. Ramin Najafi and Stephen Hecht in connection with this litigation.[1] Specifically, I have been asked to evaluate opinions by Drs. Najafi and Hecht regarding the state of knowledge in the field of chemistry, and in particular by chemists involved in the development and manufacture of drug substances, regarding the potential for formation of nitrosamines in valsartan drug substance manufactured by Zhejiang Huahai Pharmaceutical Co., Inc. ("ZHP") prior to the discovery of trace amounts of N-nitrosodimethylamine ("NDMA") in the drug substance in 2018. My opinions and responses to Drs. Hecht and Najafi are set forth below.

I. QUALIFICATIONS

I completed a B.S. in Organic Chemistry at the State University of New York at Buffalo in 1979. I subsequently completed a Ph.D. in Synthetic Organic Chemistry at the University of Pennsylvania in 1985 and a postdoctoral degree in Synthetic Organic Chemistry at the University of California at Irvine in 1987, where I was awarded a National Institute of Health postdoctoral fellow scholarship.

[1] It is my understanding that the expert opinions in the reports submitted by Drs. Najafi and Hecht are referenced and relied upon by experts offering opinions specific to the case of plaintiff Gaston Roberts, including, for example, Dr. Fareeha Siddiqui, M.D., Dr. John A. Russo, M.D. and William R. Sawyer, Ph.D. It is also my understanding from these reports that Mr. Roberts alleges that he was exposed to valsartan medications that included trace amounts of NDMA, not any other nitrosamine impurity. As a result, I limit opinions and critiques to the issue of NDMA in ZHP's valsartan API.

I started my professional career in 1987 as a Process Chemist at Merck Research Laboratories ("Merck"), where I was responsible for developing the synthesis of active pharmaceutical ingredients ("APIs"). In 1996, I founded J-STAR Research, Inc., a leading process research company, where I served as the President and CEO until March 2023. As the founder and CEO of J-STAR, I built and put into place the groups required to prepare and deliver API (including GMP-grade API for use in humans), on behalf of pharmaceutical clients, to drug product manufacturers. One group was responsible for material preparation (the "Synthesis Group") and another group was responsible for analytical testing (the "Analytical Group"). The Analytical Group included an Impurity Isolation and Identification sub-group. This sub-group was responsible for isolation of process impurities and identifying their chemical structure by spectroscopic means such as multi-nuclear Nuclear Magnetic Resonance and Mass Spectroscopy (high and low resolution). At the time of my retirement at J-STAR, the company employed approximately 150 people, including approximately 70 process chemists, whom I supervised and oversaw—both directly and indirectly—in my role as the leader of all operations in the United States.

Over the last 38 years, I have operated as an organic chemist and pharmaceutical process research chemist, primarily with respect to the development of drug substance/API. Much of my effort has been dedicated to evaluating and implementing new synthetic processes to prepare APIs, as well as evaluating and implementing changes to the steps used to prepare API. When nitrosamines were discovered in various drug substances, including generic valsartan, around 2018, I became involved in evaluating and implementing various analytical procedures for detecting nitrosamines in drug substances. Through this experience, I gained substantial knowledge regarding potential routes for nitrosamine formation and methods sensitive enough to identify and quantify nitrosamines potentially present in API.

My CV is attached as Exhibit 1 to this report. I am being compensated at a rate of $400 per hour for my work in this case.

II. BASIS FOR OPINIONS

My opinions in the case are based on my education in the fields on Organic Chemistry and Synthetic Organic Chemistry, as well as my 38 years as a process chemist working in the pharmaceutical industry. My opinions are also based on my review and analysis of materials related to this case, including the following expert reports and source materials cited therein:

- Report submitted by Stephen S. Hecht, Ph.D., dated July 6, 2021.
- Supporting exhibits, references, and literature cited in Dr. Hecht's July 6, 2021 report.
- Report submitted by Stephen S. Hecht, Ph.D., dated October 31, 2022.
- Supporting exhibits, references, and literature cited in Dr. Hecht's October 31, 2022 report.
- Report submitted by Ramin Najafi, Ph.D., dated October 31, 2022.
- Supporting exhibits, references, and literature cited in Dr. Najafi's report.
- Amended Report submitted by Ali Afnan, Ph.D., dated January 11, 2023.
- Supporting exhibits, references, and literature cited in Dr. Afnan's report.
- August 18, 2021 Deposition of Stephen S. Hecht, Ph.D., and exhibits.
- January 13, 2023 Deposition of Stephen S. Hecht, Ph.D., and exhibits.

- January 18 & 24, 2023 Depositions of Ramin Najafi, Ph.D.

A list of the materials I considered is attached as Exhibit 2 to this report. I reserve the right to update and/or modify my opinions to the extent additional information becomes available.

III. OPINIONS

Over the course of my 38 years of work in the pharmaceutical and drug development industry, I have been involved in the development of more than 250 APIs. In developing every one of the API substances I worked with over course of my career, I—and my team—made an effort to anticipate impurities that may form in the production of the drug substance. For example, after 2015, when ICH M7—addressing genotoxic impurities—was adopted by the FDA, the potential formation of genotoxic impurities was a consideration with respect to every API that we developed. It is impossible, however, for any drug substance developer or manufacturer to anticipate, in advance of production, every impurity (including genotoxic impurities) that may form in a drug substance based solely on a review of the manufacturing components and processes. This is because the world of potential impurities, and the mechanisms by which they can form, in any drug substance is nearly infinite, and trace and sub-trace amounts of countless impurities can be present in any drug substance. Further, the formation of low-level, trace impurities in drug substances is often the result of multi-step processes, by non-typical, minor reaction pathways in which drug components interact, often in unexpected ways, in the different reactions used in the development and manufacturing processes. It is therefore inaccurate, as a matter of science and basic logic, to suggest that it is possible for a chemist—or drug substance development lab—to anticipate the formation of all, or even a majority, of previously-unknown impurities in a drug product based on general chemistry knowledge. This is also true in circumstances in which a change is made to the process for manufacturing drug substances. In my experience, most trace impurities that appear during the research and development phase for a drug substance are unexpected. At my lab, we were generally alerted to the presence of impurities by the observation of new peaks on a chromatogram that were above the identification threshold of 0.10%.

As explained in the report of Dr. Najafi, NDMA formed in valsartan API as a result of certain changes to the valsartan manufacturing process made in the 2010-2013 timeframe. (*See* Najafi Rep. at 19-26.) In April 2012, ZHP changed Step 4 of the valsartan manufacturing process, which involved the catalyst triethylamine hydrochloride ("TEA"), to add a quenching process using sodium nitrite to address safety concerns about residual sodium azide in the reaction mixture. (*See, e.g.*, PRINSTON00071518-527; ZHP02563327 at -390.)) In addition, a December 2013 change to the process added the widely used solvent dimethylformamide ("DMF"). (*See, e.g.*, PRINSTON00073102-119; ZHP02563327 at -390).) Drs. Hecht and Najafi assert that these changes, together, resulted in the formation of NDMA in valsartan API.

Both Dr. Najafi and Dr. Hecht opine that ZHP should have known or suspected prior to 2018 that these changes would lead to formation of trace amounts of NDMA as an impurity in valsartan API because: (1) nitrosamines were expected impurities in drug substances prior to 2018; (2) ZHP should have known to test its valsartan API for nitrosamines using GC-MS test methods prior to 2018; and (3) the use of sodium nitrite quenching in a reaction involving DMF solvent would have put any reasonable chemist on notice of a risk for NDMA formation prior to 2018. (Najafi Rep. at 28; 2021 Hecht Rep. at 19-20; 22; 2022 Hecht Rep. at 1-2.) As an organic chemist, and based on

my experience working in the industry as a pharmaceutical process research chemist for API during the relevant time period, I strongly disagree with each of these assertions, all of which are based on projection of current-day knowledge about NDMA formation (which Drs. Hecht and Najafi admit was developed ***as a result of*** the discovery of nitrosamines in valsartan in 2018) onto the pre-2018 time frame. And to the extent Drs. Hecht and Najafi do cite pre-2018 literature, none of those materials would have put a reasonable chemist involved in the development of drug substance on notice of the potential for NDMA formation in valsartan API.

A. Nitrosamine Impurities Such As NDMA Were Not Expected—Or Routinely Tested For—In Drug Substance Prior to 2018.

Drs. Najafi and Hecht make statements in their reports asserting or suggesting that the potential for the presence of nitrosamines in drug substance was not "unexpected" prior to the valsartan recall in 2018 (Najafi Rep. at 7; 2022 Hecht. Rep. at 5) and that ZHP "could have and should have identified the risk of formation of nitrosamines, including NDMA" and specifically tested valsartan API for NDMA (2022 Hecht Rep. at 1; *see also* Najafi Rep. at 27).

This 20/20 hindsight is inconsistent with the reality of the pharmaceutical industry's knowledge and practices in the years before the valsartan recall. To develop my opinions for this report, I analyzed literature cited by Drs. Hecht and Najafi as supposed evidence that the industry had this pre-2018 knowledge. My analysis confirmed that, prior to 2018, neither NDMA nor nitrosamines generally were known to be impurities in drug substance, and therefore, they were not expected impurities. As noted in a 2023 article, "the history of [n]itrosamines as a confounding impurity in pharmaceutical products is not very old," in that it begins in "June 2018, [when] regulatory bodies first detected the presence of these impurities in Valsartan batches[.]"[2]

After the discovery of NDMA in valsartan API, "many investigations were carried out, which detected traces of these impurities in Ranitidine, a H2 blocker used to treat acidity or stomach ulcers" and "[e]xtremely low levels were also identified in some batches of Metformin hydrochloride."[3] As a result of these discoveries, "[m]ajor pharmaceutical regulatory agencies in the world like European Medicines Agency (EMA) and US-Food and Drug Administration (US-FDA) have provided guidelines on controlling nitrosamines in human medicines for approved marketing authorization holders," have "requested all marketing authorization holders of pharmaceutical products to complete an initial risk evaluation of their respective products," and have "taken steps to provide specific and sensitive analytical methods for nitrosamine detection from drug substances and products."[4] In addition, "pharmaceutical companies are now required to monitor the presence and level of nitrosamine contamination."[5]

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[2] Akkaraju et al. "A comprehensive review of sources of nitrosamine contamination of pharmaceutical substances and products." Regul Toxicol Pharmacol. 2023 Mar:139:105355. doi: 10.1016/j.yrtph.2023.105355. Epub 2023 Feb 13.

[3] *Id.*

[4] *Id.*

[5] *Id.*

In my own substantial experience in the development of drug API, I did not expect NDMA in any of the hundreds of drug substances on which I worked prior to the discovery of NDMA in multiple drug substances around the 2018 timeframe, at which point the FDA developed an analytical testing method for NDMA in pharmaceutical substances and set a limit for the amount of NDMA permitted in drug products. *See* https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current (FDA stating that it "developed the gas chromatography-mass spectrometry (GC/MS) headspace testing method" to "help manufacturers and regulators detect NDMA in valsartan API and tablets" in 2018). It was not until after the valsartan recall (and subsequent recalls of other pharmaceutical drug products based on the discovery of nitrosamines in valsartan) that there was a broad awareness of the potential for NDMA in drug substance or product that triggered routine investigation and testing for it. Indeed, the FDA stated in multiple announcements about the valsartan recall that the presence of NDMA in valsartan was unexpected by both industry and regulators.[6]

Prior to 2018, my lab (which as noted included 70 process chemists among many other scientifically knowledgeable employees) never considered the possibility of NDMA formation in the intermediates or API we prepared. My lab never encountered a stable nitrosamine, like NDMA, that was capable of being isolated. After the Valsartan recall in 2018, the potential for formation of nitrosamines, including NDMA, became one of the most important and discussed topics in the industry. Seminars were given, panel discussions were happening at trade shows that I attended (such as Chem Outsourcing in Parsippany, New Jersey), and company training for nitrosamine education became standard. It remained a hot topic for years. Test methods for NDMA detection and low-level quantitation became available. Analytical contract labs began advertising the ability to test for NDMA. At that point, all or nearly all of J-STAR's customers (nationwide) began to inquire about the company's strategy for nitrosamine risk mitigation and testing. Discussion of the issue of nitrosamines in drug substance, including their potential formation, prevention, and appropriate analytical testing, is now a widespread, commonplace industry standard—but was not prior to 2018.

The literature cited by Drs. Hecht and Najafi does not support their position that organic chemists in the pharmaceutical industry knew of the need to test drug substance for nitrosamines such as NDMA prior to 2018. For example, Dr. Hecht cites the 1978 IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans as evidence that the reactions leading to NDMA and the use of mass spectrometry to identify NDMA has been widely known for many years. (*See* 2022 Hecht Rep. at 1; 2021 Hecht Rep. at 18.) However, IARC monographs are not a source of literature on which process chemists are trained; nor are they used in our work. It is not reasonable to expect that any process chemist at ZHP or elsewhere would seek out this literature prior to the first observation of a nitrosamine impurity in API in 2018. In addition, the

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[6] *See* https://www.fda.gov/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity; https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current; https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps.

section of this monograph that discussed NDMA, which appears 125 pages into the publication, does not reference DMF solvent or state that it can lead to the formation of NDMA. And the only reference to GC-MS testing for NDMA relates to a 1977 US Environmental Protection Agency ("EPA") notice requiring registrants of pesticide products "potentially contaminated with N-nitroso compounds to analyze commercial samples" of those products with GC-MS or other methods such as high-pressure liquid chromatography "to determine the extent of contamination."[7] A statement that the EPA required GC-MS or other testing for ***pesticide*** products specifically suspected of being contaminated with NDMA does not suggest that chemists developing drug substances approximately 30 years later should have known to conduct routine GC-MS testing on valsartan API to look for NDMA.

Other cited articles and publications, including a 1956 article by Magee and Barnes, merely speak to the general carcinogenic or genotoxic potential of nitrosamines, but no reasonable chemist would conclude—based on this information—that nitrosamines were expected in the valsartan manufacturing process because of the potential for the multiple reactions that ultimately resulted in the formation of NDMA. (2021 Hecht Rep. at 4-5; 2022 Hecht Rep. at 4.) And while Dr. Hecht cites articles, such as Ender et al. 1968, that discuss the identification of NDMA in food or tobacco products, these sources would not have put process chemists on notice of the particular sequence of reactions that caused nitrosamines to form in valsartan API. (*See id.*)

I have also reviewed a 2017 email from Dr. Jinsheng Lin at ZHP, heavily relied on by plaintiffs' experts. (*See* Najafi Rep. at 30; 2021 Hecht Rep. at 19-20; 2022 Hecht Rep. at 7-8.) It is difficult to interpret this email. As I understand it, in the email, Dr. Lin appears to be comparing an unknown impurity identified during the testing of a proposed manufacturing change to irbesartan, a different drug substance, to other known impurities. In particular, Dr. Lin compares the unknown impurity in irbesartan to Impurity K, a known impurity in deacylated valsartan. (*See* ZHP-296 (English translation attached as Ex. ZHP-296 to 4/20/21 Deposition of Min Li ("4/20/21 Li Dep.")).) Deacylated valsartan is not the same as valsartan API. These two molecules have different chemical structures. Specifically, deacylated valsartan is missing the pentanoyl side chain that is present in valsartan API. The email attaches a patent application for deacylated valsartan that addresses Impurity K and supports the comparison being made in the email. (*See* ZHP-469A (English translation attached as Ex. ZHP-297 to 4/20/21 Li Dep.).) The email also includes Dr. Lin's theory on how this unknown impurity in irbesartan may have formed, and the structure of the unknown impurity in irbesartan that is drawn by Dr. Lin is structurally similar to the structure of Impurity K. Given that the substance of the email is about irbesartan, and the attachment describes deacylated valsartan and Impurity K, Dr. Hecht's and Dr. Najafi's interpretation of the phrases "N-nitrosodimethylamine that occurs in valsartan" and "its structure is very toxic" makes no sense.

B. <u>The Test Methods For Identifying And Measuring NDMA In Pharmaceutical Drug Substance Were Not Developed By The FDA Until After The Valsartan Recall.</u>

[7] International Agency for Research on Cancer (1978) Some N-nitroso compounds, In IARC Monogr. Eval. Carcinog. Risk Chem. Hum. pp 83-175, IARC, Lyon, FR.

I also disagree with the assertions of Drs. Najafi and Hecht that ZHP should have known to use GC-MS technology to test its valsartan API for NDMA formation prior to 2018.

Dr. Najafi claims that "ZHP provided no explanation for why GC-MS, a workhorse technique used by organic chemists for decades and which is available in many undergraduate chemistry labs and common in pharmaceutical laboratories, was not used to analyze [for nitrosamine] impurities in valsartan after a process change." (Najafi Rep. at 28; *see also id*. at 12; 2022 Hecht Rep. at 6.) These statements are once again based entirely on hindsight and are inconsistent with the knowledge of, and established testing methods used by, the pharmaceutical industry prior to the valsartan recall. As detailed in the Amended Report of Dr. Ali Afnan, ZHP tested its valsartan API for impurities using gas chromatography with flame ionization detection ("GC-FID") consistent with the procedures set forth in accordance with the United States Pharmacopeia ("USP") monograph on valsartan and USP's standards for testing for residual solvents. (*See* Afnan Rep. ¶¶ 173-79.) It was not until after NDMA was first discovered in valsartan API in 2018 that the FDA developed a "gas chromatography-mass spectrometry (GC/MS) headspace method to detect the presence of NDMA . . . in valsartan" and other different drug substances. (*Id*. ¶ 182.) Drs. Najafi and Hecht do not dispute this. (*See* Najafi Rep at 9 (noting that it "[i]n response to the detection of nitrosamines found in valsartan containing medications [that] the FDA published testing methods with several options for industry, as well as regulators, to test for nitrosamines, including NDMA").)

Neither Dr. Najafi nor Dr. Hecht points to any scientific literature or industry guidance prior to 2018 stating or suggesting that pharmaceutical laboratories use GC-MS to test drug substance for nitrosamines. Instead, they suggest that the fact that GC-MS was generally available prior to 2018 suggests that ZHP should have been using it all along. But prior to 2018, GC-MS would not have been the standard for routine residual solvent analysis used in API release testing. Since nitrosamines were not detected or expected in API prior to 2018, it is not reasonable to suggest that a non-routine instrument such as GC-MS should have been procured and used to test for them. Drs. Najafi and Hecht present no evidence, and I am not aware of any, that GC-MS was routinely used in the pharmaceutical industry for nitrosamine detection before 2018.

Dr. Hecht refers to a single 1976 publication by Magee et al. that states "gas-liquid chromatography and mass spectrometry" have "yielded more reliable identification of the nitrosamines." (2022 Hecht Rep. at 4.) Dr. Hecht also states that GC-TEA "gave way to GC-MS" as a standard testing mechanism in the early 1980s, but he does not cite any literature to support this statement. (*Id.*) Instead, he points to: (1) the fact that the American Society for Mass Spectrometry holds annual conferences at which GC-MS is discussed; and (2) former students who went on to work in industry and have told him that pharmaceutical companies have mass spectrometry capabilities. (*See* Hecht 1/13/23 Dep. 146:3-19, 144:8-24.) This is not adequate information from which to conclude that GC-MS was the industry standard for residual solvent testing in valsartan API, or other drug substances, prior to 2018, especially because it does not match my experience in the field. At J-STAR, we tested residual solvents for API release testing using headspace GC-FID during my entire tenure there.

In addition, Dr. Hecht himself has not worked for a pharmaceutical company and it appears that he admitted at his deposition that he does not know whether or how long mass spectrometry has been widely used in the pharmaceutical industry. (*See* Hecht 1/13/23 Dep. 285:1-9 ("I don't

really have facts to back that up."). Further, it is notable that even Novartis, the potential customer that first identified the impurity peak that turned out to be NDMA in 2018, was not using GC-MS for its qualification of ZHP-supplied valsartan—and instead had to go to an outside laboratory, Solvias AG, for GC-MS testing once the peak was observed. (*See* Afnan Rep. ¶¶ 104-105.)

C. The Use Of DMF Solvent In A Reaction With Sodium Nitrite Would Not Have Alerted A Reasonable Chemist To The Potential For Nitrosamine Formation Prior To 2018.

Drs. Hecht and Najafi also state that any reasonable chemist would have suspected the possibility of nitrosamine formation from the valsartan manufacturing processes at issue because they used sodium nitrite and DMF solvent. (Najafi Rep. at 27; 2022 Hecht Rep. at 1.) Again, neither expert cites to any literature, prior to 2018, demonstrating that sodium nitrite and acid will react with DMF to directly form nitrosamines. As Drs. Najafi and Hecht acknowledge, formation of nitrosamines requires a reaction between nitrous acid and a ***secondary amine*** (*see* Najafi Rep. at 7; 2022 Hecht Rep. at 5) and DMF solvent is not a secondary amine.

In the valsartan processes that resulted in trace amounts of NDMA in the API, the secondary amine was dimethylamine ("DMA"), which will react with nitrous acid to form the NDMA. But the valsartan manufacturing process, as designed, did not directly involve either nitrous acid or DMA. Instead, as Dr. Najafi explains, the sodium nitrite used in the quenching process reacted with acidic conditions in the reaction to become nitrous acid. (Najafi Rep. at 26.) In addition, the common laboratory DMF solvent decomposed into the secondary amine DMA and reacted with the nitrous acid to become NDMA. (*See* Najafi Rep. at 33.) Based on the information known to me, as a research process chemist developing drug substances, prior to 2018, I would not have expected the decomposition of DMF into DMA and the subsequent nitrosation of DMA during the quenching process to form NDMA.

Drs. Hecht and Najafi state that these multiple, cascading reactions were reasonably foreseeable to any educated chemist. (*See, e.g.* Hecht Rep. at 1 ("[q]uenching the sodium azide with sodium nitrite (nitrous acid) in the presence of the product . . . led to a reaction between foreseeably created secondary amines and the nitrous acid to create NDMA/NDEA").) But those opinions were formed with the benefit of hindsight, knowing now that nitrosamines ***can*** form in valsartan API, understanding exactly ***how*** NDMA did form in the drug substance, and then working backward to find scientific support to explain how each step of the reactions that led to NDMA formation occurred. Neither ZHP, nor any process chemist, had this benefit of hindsight in developing the drug substance. If I had reviewed valsartan's API manufacturing process steps and components prior to 2018, I would not have expected that nitrosamines would or could form in valsartan API. Indeed, as explained in Dr. Afnan's report, chemists at the FDA reviewed the Drug Master Files for valsartan API that detailed the manufacturing processes and changes at issue and did not raise any concerns about nitrosamine formation prior to 2018. (*See* Afnan Rep. ¶¶ 66-67; 76-79.)

The scientific literature cited by Drs. Najafi and Hecht does not support their assumption that reasonable chemists were on notice prior to 2018 that NDMA could form in valsartan API. Drs. Najafi and Hecht both rely on the Purification of Laboratory Chemicals, Armarego, WLF (4th Edition 1996; 6th Edition 2009) to opine that "[u]sing DMF solvent in the process should have raised concern for the possible formation of nitrosamines because DMF solvent has been long

known to decompose into dimethylamine." (Najafi Rep. at 26; *see also* 2022 Hecht Rep. at 5.) But this textbook merely mentions that DMF could decompose "at its boiling point to yield dimethylamine." (*See* Ex. 24 to 1/13/24 Dep. of S. Hecht.) Neither Dr. Hecht nor Dr. Najafi cites evidence that the valsartan manufacturing process was run at the boiling point for DMF. Further, chemists purchasing DMF that is already pure grade, from a qualified supplier, would not be consulting an undergraduate-level handbook outlining how to purify the solvent, especially because DMF is a well-known and widely used solvent in process chemistry and API manufacturing processes. In my experience as a chemist who has long worked with DMF solvent in processes for developing drug substances, the focus of a chemist using DMF is on how well the desired reaction performs using the solvent, as well as isolating the desired product from the DMF reaction mixture. The quenching process will turn the DMF into a waste stream (typically in a separated aqueous phase containing inorganic salts), and minor reactions taking place in a waste stream are not a significant focus.

Dr. Hecht cites a 2009 article entitled "DMF, Much More Than a Solvent," which states that DMF decomposes "slightly at its boiling point to afford dimethylamine" with the reaction possible at room temperature in the presence of acidic or basic materials. (2022 Hecht Rep. at 5.) But the focus of that article is on the properties and virtues of DMF, a solvent that is used in a number of complex syntheses and is capable of dissolving many compounds. The article does not suggest that use of DMF can lead to the formation of nitrosamines.

Dr. Hecht also indicates that DMA exists as an impurity in DMF but cites no evidence that this was something that ZHP chemists knew or had reason to investigate prior to 2018. (*See* Hecht 2022 Rep. at 3.) Dr. Hecht states that ZHP employee "Jun Du testified . . . 'it is not the residual DMF that reacts with nitrous acid of the next step, but rather it is the trace amount of dimethylamine, an impurity/degradant of DMF that reacts with the nitrous acid to form NDMA . . ." (*Id.*) But Mr. Du expressly testified that he, and ZHP, gained this knowledge ***in 2018*** in the process of investigating the route by which NDMA formed ***after*** it was discovered. (*Id.*) Mr. Du explained at his deposition that the fact that ZHP was not aware of the possibility that DMA could be introduced into the valsartan manufacturing process "obscured us from foreseeing this impurity during the process change from triethylamine process to zinc chloride process" prior to 2018. (*Id.*) This is consistent with my substantial experience in investigating and identifying the cause of impurities in drug substance over the course of my career. As explained above, once an impurity over the relevant investigation threshold is identified, chemists can work backwards to determine the mechanism by which the impurity developed and how it can be prevented in the drug substance. This process of investigating an impurity provides chemists with new knowledge and information that often could not have been reasonably foreseen prior to the impurity being identified, often due to the complex and multi-step nature of the chemical reactions involved in creating drug substances.

In short, at the time that ZHP was using DMF solvent to manufacture valsartan, it was a widely popular solvent used routinely in API manufacturing processes. In my experience, it was not a well-known concern within the pharmaceutical industry that DMF solvent could include, or degrade into, the secondary amine DMA prior to the valsartan recall. Further, the possibility of nitrosamine formation directly from DMF in a manufacturing process that included NaN3 (sodium azide) and $NaNO_2$ (sodium nitrite), which could give off the nitrous acid necessary to form nitrosamines, was not reasonably expected at that time. To the contrary, these reactions only

became widely known to research chemists in the pharmaceutical industry because of the valsartan recall leading to this litigation. In my substantial experience and work in the pharmaceutical industry, the use of DMF solvent—even in the context of a reaction involving sodium nitrite—would not have raised a concern about nitrosamine formation among reasonable process chemists until after the valsartan recall.

IV. CONCLUSION

The opinions offered by Drs. Hecht and Najafi regarding what ZHP should have known, prior to 2018, regarding the potential for NDMA formation in valsartan API are unsupported by scientific evidence and are inconsistent with the knowledge, general practice, and concerns held by chemists in the pharmaceutical industry at that time. It was not until ***after*** trace amounts of nitrosamines were identified in valsartan in 2018—and ZHP and the FDA worked backward to determine how they formed—that chemists working in the production of drug substance became familiar with and concerned about the possibility of NDMA in drug substance. In addition, there was no test method developed or validated to identify or quantify NDMA in drug substance before the valsartan recall in 2018.

I hold these opinions to a reasonable degree of scientific certainty.

Signed on April 10, 2025 by:

Andrew S. Thompson

Dr. Andrew Thompson, Ph.D.

Exhibit 1

CURRICULUM VITAE

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PROFESSIONAL AND ACADEMIC EXPERIENCE

1996-2023 Founder-President and CEO of J-STAR Research, Inc.

1987-1995 Process Chemist at Merck Research Laboratories, Dept. of Process Research

1985-1987 Post-Doctoral, Synthetic Organic Chemistry, University of California, Irvine

1980-1985 Doctorate, Synthetic Organic Chemistry, University of Pennsylvania

1975-1979 Bachelors of Science, Organic Chemistry, SUNY Buffalo

MEMBERSHIPS

1981-Present Member - American Chemical Society

PATENTS

Yang DJ, Yu D, **Thompson AS**, Rollo FD. Efficient Synthesis of Chelators for Nuclear Imaging and Radiotherapy: Compositions and Applications. Patent No. 10,814,013 (2020).

Savage PB, Jacks TE, Miller RA, **Thompson AS**, Randall JL. Methods for the Synthesis of Ceragenins. Patent No. 10,370,403 (2019).

Tomesch JC, Li P, Yao W, Zhang Q, Beard JD, **Thompson AS**, Cheng H, Wennogle LP. Pharmaceutical Compositions Comprising ((6BR,10AS)-1-(4-Fluorophenyl)-4-(3-Methyl-2,3,6B,9,10A-Hexahydro-1H-Pyrido[3',4':4,5]Pyrrolo[1,2,3-DE]Quinoxalin-8(7H)-YL)Butan-1-One Or Pharmaceutically Acceptable Salts Thereof. Patent No. 10,464,938 (2019).

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Exhibit 2

EXHIBIT 2

MATERIALS CONSIDERED IN THE EXPERT REPORT OF ANDREW THOMPSON, Ph.D.

DEPOSITION TRANSCRIPTS:

- 2021.08.17 Deposition Transcript of Hecht, Stephen with Exhibits
- 2021.08.18 Deposition Transcript of Hecht, Stephen with Exhibits
- 2023.01.18 Deposition Transcript of Najafi, Ramin (Ron) with Exhibits
- 2023.01.24 Deposition Transcript of Najafi, Ramin (Ron) with Exhibits

EXPERT REPORTS:

- 2021.07.06 Expert Report of Stephen S. Hecht, Ph.D and materials cited therein
- 2022.10.31 Expert Report of Ramin Najafi, Ph.D and materials cited therein
- 2022.10.31 Expert Report of Stephen S. Hecht, Ph.D and materials cited therein
- 2023.01.11 Amended Expert Report of Ali Afnan, Ph.D and materials cited therein

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- U.S. Food & Drug Administration, FDA Statement on FDA's ongoing investigation into valsartan impurities and recalls and an update on FDA's current findings (August 30, 2018), https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current
- U.S. Food & Drug Administration, FDA Statement on the FDA's ongoing investigation into valsartan and ARB class impurities and the agency's steps to address the root causes of the safety issues, https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps

OTHER MATERIALS

- Akkaraju, Harshita, et al. "A comprehensive review of sources of nitrosamine contamination of pharmaceutical substances and products." Regulatory Toxicology and Pharmacology 139 (2023): 105355
- ZHP00190573-574 (English translation attached as Ex. ZHP-296 to 4/20/21 Deposition of Min Li)
- ZHP01812101-109 (English translation attached as Ex. ZHP-297 to 4/20/21 Deposition of Min Li)